REMARKS

In the Office Action dated May 11, 2009, the Examiner objected to claim 1, asserted that claims 1, 3, 6 and 8 are substantial duplicates, rejected claims 1-3, 5, 6, 8, 17 – 19 and 22-28 under 35 U.S.C. § 112, first paragraph, for non-enablement, rejected claims 1, 5, 6, 8, 17 – 21 and 28 – 29 under section 112, first paragraph, for lacking a written description, and rejected claims 1, 5, 6, 8, 9, 14 – 21, 28 and 29 as obvious over Capecchi in view of Seth.

Claim Objection

The language noted by the Examiner in the preamble of claim 1 has been deleted. The objection is thereby overcome.

Double Patent Warning

The provisional double patenting warning has been addressed by amendment of claim 1 to provide that the mouse is homozygous for the mutation and by cancelling claims 3, 6 and 8.

35 USC § 112, 1st paragraph – Non-enablement

Claim 1 has been amended to limit the claim to a homozygous mouse. The heterozygous mouse is therefore excluded from claim 1 and from the claims which depend from claim 1, in particular claims 17 – 19 and 28. The rejection as to any cell heterozygous for disruption and behaving like a wild type cell is thereby overcome.

Claim 21 is amended to remove the dependency on claim 1. Claim 21 therefore encompasses a process of obtaining a heterozygous mouse as the product directly obtained by the process.

35 USC § 112, 1st paragraph – Written Description

As noted above, claim 1 is amended to provide a transgenic mouse homozygotic for the mutation. Applicants submit that the rejection is thereby overcome.

35 USC §103(a)

The prior art rejection has already been raised and overcome.

An obviousness rejection over the combination of Capecchi in view of Seth was made in the office action of June 28, 2006 (see page 15 of the action rejecting claims 9 – 21 and 29).

In the Amendment C filed on December 27, 2006, Applicants amended the claims and submitted arguments to overcome the obviousness rejection.

In the action of April 11, 2007, the Examiner again rejected some claims over the combination of Capecchi and Seth, but also indicated that claims 13 and 30 were directed to allowable subject matter.

Following a telephone interview with the Examiner that included a discussion of the section 103 rejection, Applicants filed an amendment on August 7, 2007, amending claim 1 to include the limitations of claim 30 and amending claim 9 to include the limitations of claim 13, thereby overcoming the 103 rejection.

Following the addition of the allowable limitations into claims 1 and 9, the Examiner issued an Action on August 7, 2007, rejecting the application on other grounds but no longer raising a prior art rejection under either section 102 or 103 over Capecchi and Seth or any other prior art.

In the action of December 31, 2007, the obviousness rejection was also not asserted by the Examiner.

In an action on August 19, 2008, no prior art rejection was raised by the Examiner.

Surprisingly, and to Applicants' strong protest, the Examiner again raises the issue of obviousness over Capecchi in view of Seth in the action of May 11, 2009. The combination of Capecchi and Seth is being applied against claims 1 and 9 and the claims which depend therefrom, the very claims which were amended more than two years ago to overcome the rejection and the claims which were not rejected over the art in three subsequent actions from the Examiner. This rejection has therefore been raised, extensively argued and overcome long ago. The obviousness rejection is therefore in error.

The clamed invention is non-obvious over the combination of Capecchi and Seth.

Capecchi teaches a vector to be used to produce knockout mouse. In particular, it teaches a targeting vector having a first and a second segment of homologous sequences and a positive selection marker between the two homologous sequences. Furthermore, it teaches various markers that can be used to produce transgenic animals and that these vectors can be used to produce transgenic animals, wherein ES cells are the target cells and wherein the vector can then

be introduced into ES cells by electroporation or microinjection. These transformed ES cells can then be combined with a blastocyst and then grown and contribute to the germ line of the resulting chimeric animal. Capecchi also teaches that cell line from the animals can be used to characterize gene function or be used in assays. From the examiner's viewpoint, Capecchi shows that these vectors and methods can be used to determine the biological function of any known gene of interest. Capecchi does not teach, however, the sequence of the sigma receptor of the instant invention.

Seth teaches that cDNA sequences of Sigma-1 receptor, a known sequence that would fulfill the limitations of the claim because this sequence would be considered homologous to at least a portion of the endogenous sigma receptor.

The examiner's conclusion that it would have been obvious to a skilled person to modify the homologous sequences in targeting vectors as taught by Capecchi, with segments of DMA for Sigma-1 receptor by isolating and using the genomic segment taught in Seth and to make a targeting construct and use said construct to generate a gene disrupted mouse, and further breed them to generate homozygous gene disrupted mice lacking detectable levels of said receptor, is incorrect. Similarly, the examiner's additional conclusion, that one would have been motivated to use the method of making a targeting vector and producing mice having homozygous disruption of sigma receptor and that one would have reasonable expectation of success of making and using sigma receptor gene disrupted mouse as prior art fully provides the requisite teaching, suggestion and motivation to make and use said gene disrupted mouse, leading to prima facie obviousness, is also incorrect.

Applicants submit that the examiner is carrying out an "ex post facto" analysis when assessing obviousness. The Examiner is in error in stating that "one would have reasonable expectation of success of making and using sigma receptor gene disrupted mouse". Although Sigma-1 receptor gene was known and "knock-out" technology was an established technology, when a "knock-out" project begins there are no reasonable expectation of success as expressed by the examiner. In this regard many arguments explaining this fact were already filed in the response of December 2006 which are still maintained.

The fact that there are no reasonable expectations of success is a general rule for any knock out project since it is not evident whether a certain genetic deficiency would be viable or

not. In the case of Sigma-1 KO mouse the expectation of success was a priori even lower since Sigma-1 receptor is a gene ubiquitously expressed (see for example Seth et al page 535 first paragraph or last paragraph of page 1 bridging to page 2 of the present application). In particular it is important to note that Sigma-1 receptor is expressed in ovary testicles and placenta.

A skilled person considering the possibility of generating a knock-out mouse would avoid the inactivation of a gene expressed in so many tissues as it is very likely that the resulting animal results in a non-viable animal. In particular, a skilled person would avoid the inactivation of a gene which is expressed in ovary, testicle and placenta since it seems a priori very likely that even if viable the animal will have fertility problems. Of course a KO mouse is interesting as a model system if they are viable as homozygous mutants and if they are fertile, otherwise they are not interesting.

Thus, the Sigma KO project contained a priori many technical hurdles which make a priori think that the expectation of success was very low.

Apart from this specific hurdles that Sigma-1 gene presented, in the generation of a KO mouse, there is a factor which is well known to a skilled person to be critical and unpredictable: the frequency of recombination. This factor is so important that makes it impossible to generate a KO for certain genes. In the generation of Sigma-1 KO mouse the inventors of the present application first designed a homologous recombination called pHR53 identical to pHR53 TK but without the TK gene as negative selection. This strategy has been used successfully by other research group in the preparation of KO mice (for example Kaestner et al.). They tried this vector in CK35 ES mice cells (obtained from Inst. Pasteur, Paris) because it is simpler than targeting vectors with negative selection markers and because they can accommodate more homologous sequences of the targeted locus. Moreover the treatment of ES cells with potentially dangerous drugs such as ganciclovir for the negative selection can alter ES cell properties for example by compromising their pluripotency and germ line transmission. From 561 recombinant ES cells clones transformed with pHR53 vector none of them showed the inactivation of the gene thus the efficiency of recombination was 0%. This represented a real hurdle since from 561 clones tried it was expected that at least one of them incorporated the mutation. The frequency of recombination of Sigma-1 gene was so low to the feasibility of the project was seriously jeopardized. At this point probably many groups would have abandoned the Sigma-1 KO project

since they would have thought that at this point the expectation of success were indeed completely lost.

Notwithstanding, the inventors of the present application continued with their investigation despite the very poor expectations of success. They changed the CK35 ES cells by R1 ES mice cells obtained from Mount Sinai in Toronto and they included as negative selection marker a TK gene (there are many other ES cell lines as well as other negative selection genes such as difterin toxic gene). In this round of transformation using the new recombination vector in the new ES cell line, the frequency of recombination surprisingly raised until 4,4%. This unexpected result allowed the final generation of the Sigma-1 KO-mice disclosed in the present application.

The specification sets for an example of the generation of the mouse deficient in the Sigma-1 receptor gene beginning in paragraph [0093] through paragraph [0111]. From 9.6×10^6 transfected cells, 272 recombinant closes of mouse cells ES were analyzed. Of the 272, 12 showed the expected polymorphisms. Following this, four recombinant clones were selected. These were aggregated with embryos in the eight cell stage to provide 282 aggregated and transferred embryos, of which 40 advanced in gestation, of which 11 chimeras survived. The 11 chimeras correspond to two clones of independent ES cells. Four of the chimeras were able to transmit the ES cell genotype. Crossing of heterozygous types was carried out to obtain homozygous types.

Therefore, it is noted that despite knowledge of the knock-out generating technology from Capecchi and the knowledge of the Sigma-1 KO mouse, the preparation of a Sigma-1 KO mouse was not obvious due to the lack of reasonable expectations of success.

The generation of this KO mouse was possible thanks to the high ingenuity of the scientific team which was capable of developing an inventive recombination vector which is deposited under access number CECT 5737.

Claim 1 of this application is limited to a mutant mouse lacking detectable levels of Sigma-1 receptor obtainable by the use of the non-obvious vector pHR53TK deposited according to the Budapest treaty under the deposit number CECT 5737.

As such, the claimed invention is non-obvious over the cited prior art, whether considered alone or in combination, so that the prior art rejection is overcome and should be withdrawn.

Conclusion

Each issue of the action has been addressed and the application has been placed into form for immediate allowance. In view of the amendments to the claims and the remarks set forth above, the Applicants respectfully submit that the present invention is in condition for allowance.

Deposit Account Information

The Commissioner is hereby authorized to charge any additional fees which may be required or to credit any overpayment to account no. 501519.

Respectfully submitted,

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